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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1609	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,282	BENAMEUR ET AL.	
	Examiner	Art Unit	
	Aradhana Sasan	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 June 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks filed on 06/13/2007 are acknowledged.

2. Claims 14-28 are included in the prosecution.

Response to Arguments

3. Rejection of claim 14 under 35 U.S.C. § 112, first paragraph

Applicants' arguments, see Pages 6-7, filed 6/13/07, with respect to the rejection of claim 14 under 35 U.S.C. § 112, first paragraph as being enabling for a statin as a water insoluble active, but not enabling for any active principle have been fully considered but are not persuasive. Applicants argue that the specification enables the composition for any principle, as demonstrated by example 4. However, the only active ingredient used in the working examples is simvastatin. Applicants' assertion that Example 4 demonstrates that the microemulsion area increases significantly when CAPRYOL 90 or CAPRYOL PGMC are used as surfactant, regardless of the active ingredient, is not substantiated by using active ingredients different from simvastatin. Any active ingredient will not interact with the lipophilic/hydrophobic phase of the composition because not all active ingredients have this property. Undue experimentation would be required to use any active principle with the invention.

4. Rejection of claims 14-17, 24-25, and 27 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136)

Applicants' arguments, see Pages 7-8, filed 6/13/07, with respect to the rejection of claims 14-17, 24-25, and 27 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136) have been fully considered but are not persuasive.

Applicants argue that Farah does not teach the use of propylene glycol monocaprylate as a co-surfactant and does not suggest any motivation to use caprylic esters of propylene glycol as a co-surfactant. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Farah teaches co-surfactants chosen from the group comprising lauric esters of propylene glycol, oleic esters of polyglycerol and ethyl diglycol (Col. 3, line 60 to Col. 4, line 4). Farah teaches that "C_8 –C_{18}-"fatty acid" denotes mixtures in significant and variable proportions of caprylic (C_8), capric (C_{10}), lauric (C_{12}), myristic (C_{14}), palmitic (C_{16}) and stearic (C_{18}) adds when these acids are saturated, and of the corresponding C_8-C_{18} unsaturated acids. The proportions of these fatty acids can vary in accordance with the starting oils" (Col. 3, lines 20-25). Although Farah does not expressly teach the use of propylene glycol monocaprylate as a co-surfactant, a "surfactant ... having an HLB of less than 16, obtained by an alcoholysis reaction of polyethylene glycol and a fraction of oil consisting of a mixture of triglycerides of fatty acids selected from the group consisting of caprylic and capric

acids..." is taught (Col. 8, lines 59-63). One with ordinary skill in the art would find it obvious to use a surfactant or a co-surfactant that is a caprylic or capric ester of propylene glycol, given the lauric ester of propylene glycol and caprylic and capric fatty acids teachings by Farah as stated above.

Applicants argue that the use of caprylic esters of propylene glycol as a co-surfactant results in an unexpected increased rate of dissolution of the active principle. This is not found persuasive because Farah teaches that "one of the main values of the invention is that, irrespective of the amount of water supplied by the gastric or intestinal physiological fluid of the human or animal body ... the mixture composed of this amount of water and the composition will form a microemulsion, enhancing the solubility of the active principle or agent, which increases the bioavailability in spite of the appreciable proportion of this physiological fluid" (Col. 4, lines 9-16). Farah teaches the use of caprylic and capric fatty acids in the surfactant composition, and provides enhanced solubility (or dissolution) and bioavailability of the active ingredient. This advantage taught by Farah would make the results of increased dissolution of the active principle an expected result.

5. Rejection of claims 18-23 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057)

Applicants' arguments, see Page 9, filed 6/13/07, with respect to the rejection of claims 18-23 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057) have been fully considered but are not persuasive. Applicants argue that Lipari discloses using propylene glycol

dicaprylate/dicaprate, propylene glycol dicaprate and propylene glycol mono and dicaprylate as a primary solvent medium and there is no disclosure of propylene glycol monocaprylate as a co-surfactant. Applicants also argue that neither reference teaches or suggests using propylene glycol monocaprylate as a co-surfactant, and that the combination of references is improper.

In response to applicants' argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, one with ordinary skill in the art would find it obvious to use propylene glycol monocaprylate given the propylene glycol mono and dicaprylate teaching of Lipari (Page 5, claim 5). One with ordinary skill in the art would find it obvious from the teaching of Farah, as discussed above, that fatty acid esters of propylene glycol, more specifically, the caprylic and capric acid esters of propylene glycol can be used as co-surfactants.

6. Rejection of claims 18-23 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057) and further in view of Patel et al. (US 6,248,363)

Applicants' arguments, see Pages 9-10, filed 6/13/07, with respect to the rejection of claims 26 and 28 under 35 U.S.C. § 103(a) as being unpatentable over Farah et al. (US 6,054,136) in view of Lipari et al. (WO 00/37057) and further in view of

Patel et al. (US 6,248,363) have been fully considered but are not persuasive. Applicants argue that there is nothing in the Patel reference that teaches or suggests the desirability of specifically using caprylic esters of propylene glycol as a co-surfactant and that Patel does not provide a single example demonstrating the use of a composition having a co-surfactant phase that includes propylene glycol monocaprylate. Applicants argue that the combination of references is improper and improper hindsight analysis was used in the rejection.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

As discussed above, one with ordinary skill in the art would find that fatty acid esters of propylene glycol, more specifically, the caprylic and capric acid esters of propylene glycol could be used as co-surfactants (based on the teaching of Farah) and use propylene glycol monocaprylate given the propylene glycol mono and dicaprylate teaching of Lipari. Patel further teaches the use of a surfactant to improve the bioavailability of simvastatin. Patel also teaches propylene glycol as a preferred alcohol, (Col. 16, lines 53-54) and the preparation of surfactants by reaction of such an alcohol

with fats or "a variety of natural and/or hydrogenated oils" (Col. 16, lines 46-49). Therefore, one with ordinary skill in the art would find it obvious to use as a co-surfactant propylene glycol monocaprylate to enhance the bioavailability of simvastatin. Regarding instant claim 26, Patel teaches the surfactant lauric macrogolglycerides as the surfactant (Col. 35, line 46, Col. 65, lines 50-53, claim 16). A person with ordinary skill in the art at the time the invention was made would have found it obvious to combine the teachings of Farah (caprylic and capric acid esters of propylene glycol could be used as co-surfactants), Lipari (propylene glycol mono and dicaprylate), and Patel (use of a surfactant to improve the bioavailability of simvastatin) because these surfactants are known in the art to work in emulsifying systems for improving bioavailability of poorly soluble drugs (like statins). Therefore, hindsight has not been employed in combining Farah, Lipari and Patel.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 14 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a statin as a water insoluble active (page 4, lines 24-28), does not reasonably provide enablement for any active principle.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue

experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claim.

The scope of the claim is broad enough to encompass the use of any active principle, not just the use of statins such as simvastatin.

The specification provides guidance for using statins as active agents in the composition because "simvastatin undergoes a strong first intestinal passage effect" (page 1, lines 10-13).

Working examples provided are directed toward compositions comprising of simvastatin (page 4, examples 1-3).

The specification does not teach that any active principle can be used in the composition. The nature of the composition is such that the active principle would have to interact with the lipophilic/hydrophobic phase and not all active principles have this property.

The nature of the invention is a composition comprising (a) an active principle, (b) a self micro-emulsifying carrier comprising of (i) a lipophilic phase, (ii) a surfactant phase, (iii) a co-surfactant phase.

The state of the prior art teaches that simvastatin is a relatively hydrophobic compound (Mauro, page 197). Igel et al. teach that, "with the exception of pravastatin and rosuvastatin, all statins are lipophilic compounds (Igel et al., page 836). It is also

taught that "all statins undergo hepatic metabolism via cytochrome P450 isoenzymes" and these isoenzymes "are the most abundant and account for approximately ... 80% in small intestinal mucosa" (Igel et al., page 838).

Undue experimentation would be required to use the invention because it is not clear which active principle is going to be used in the composition. In order to use any active principle with the invention, the quantity of experimentation would be too great.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with this claim. It would require undue experimentation to use the invention based on the breadth of these claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 14-17, 24-25, and 27 rejected under 35 U.S.C. 103(a) as being unpatentable over Farah et al. (US 6,054,136).

Farah teaches a self-microemulsifying drug delivery system (Col 1, lines 10-19). The composition is for oral use and is capable of forming a microemulsion in situ with the biological fluid of the body and comprises a pharmaceutical active ingredient, a lipophilic phase, a surfactant, and a co-surfactant (Col 8, lines 39-43, Claim 1). The surfactant is "obtained by an alcoholysis reaction of polyethylene glycol and a fraction of

oil ... consisting of caprylic and capric acids" (Col 8, Claim 1). The surfactant and co-surfactant ratio is 0.5 (Col 5, line 67). The surfactant has an HLB of less than 16 (Col 9, line 47). The lipophilic phase of the composition has an HLB of less than 16 (Col 8, lines 44-45 and lines 50-51).

Farah et al. do not teach the lipophilic phase of the composition being in the range 50%-95% by weight.

As to claim 15, Farah teaches the lipophilic phase of the composition being in the range 1%-75% by weight and having an HLB of less than 16 (Col 8, lines 44-45 and lines 50-51). The HLB of the lipophilic phase of the instant application is 14; therefore it is anticipated by Farah. Although the weight range of the lipophilic phase of the instant application does not overlap the weight range disclosed in the reference, a person with ordinary skill in the art could, without absent evidence to the contrary, arrive at the optimal weight range without undue experimentation.

As to claims 16 and 17, Farah teaches that the surfactant-co-surfactant mixtures range from 18.5%-35% of the weight of the composition (Examples 1 and 3, Col 5, lines 22-24 and lines 65-67). Although the surfactant and co-surfactant levels of the instant application do not exactly overlap the combined surfactant-co-surfactant levels of the reference, a person with ordinary skill in the art could, without absent evidence to the contrary, arrive at the optimal weight levels without undue experimentation.

11. Claims 18-23 rejected under 35 U.S.C. 103(a) as being unpatentable over Farah et al. (US 6,054,136), and further in view of Lipari et al. (WO 00/37057).

Farah teaches a pharmaceutical composition for oral use that is capable of forming a microemulsion, and comprises a pharmaceutical active ingredient, a lipophilic phase, a surfactant, and a co-surfactant (Col 8, lines 39-43, Claim 1). Farah also teaches a method of increasing bioavailability of a pharmaceutical active ingredient which is difficult to dissolve. This method includes use of the said composition. Farah does not teach statins or simvastatin as the pharmaceutical active ingredient or the use of propylene glycol monocaprylate in the co-surfactant phase.

Lipari teaches "formulations for oral administration comprising lipid regulating agents having enhanced bioavailability" (Page 3). The formulation contains propylene glycol fatty acid esters that includes propylene glycol monocaprylate (Page 3, Page 5 Claims 5 and 6). Lipari also specifically teaches the use of a statin in the formulation (Page 5, Claim 4).

Thus, a person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the pharmaceutical composition teaching of Farah with the statin formulation with propylene glycol monocaprylate taught by Lipari because of the improved bioavailability of the statin that would be conferred by the forming a microemulsion. Simvastatin is a known statin drug.

As to claims 22 and 23, a person with ordinary skill in the art could, without absent evidence to the contrary, arrive at the optimal weight of the active ingredient (simvastatin) in the composition without undue experimentation.

12. Claims 26 and 28 rejected under 35 U.S.C. 103(a) as being unpatentable over Farah et al. (US 6,054,136), Lipari et al. (WO 00/37057), and further in view of Patel et al. (US 6,248,363).

The teachings of Farah and Lipari are stated above. The emulsifying systems in these references do not specifically include lauric macrogolglycerides and caprylocapric macrogolglycerides.

Patel teaches that the bioavailability of simvastatin (Col 6, line 49) can be improved by their invention, which includes the surfactant lauric macrogolglycerides as the surfactant (Col 35, line 46, Col 65, lines 50-53, claim 16). The preferred surfactants include lauryl macrogolglycerides (Col 30, lines 45-47). The use of caprylic/capric glycerides is also disclosed (Col 17, Table 5).

Thus, a person having ordinary skill in the art at the time the invention was made would have found it obvious to combine the pharmaceutical composition teaching of Farah with the statin formulation with propylene glycol monocaprylate taught by Lipari and further combine it with the surfactants disclosed by Patel because these surfactants are known in the art to work in emulsifying systems for improving bioavailability of poorly soluble drugs (like statins).

Conclusion

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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